

Producing Structured Clinical Trial Reports Using SAS: A Company Solution

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INTRODUCTION

Boehringer Ingelheim (BI), like all pharmaceutical companies, are required to produce reports on clinical trials in order to obtain registration for new products. We adopted the European Federation of Pharmaceutical Industry Associations (EFPIA) proposal 'Structure and Content of Clinical Study Reports' as the company standard, and we have now introduced the ICH proposal. These guidelines specifies that listings of the individual patient data are given in one appendix of the report whilst summary and derived data are included in another appendix and in the main body of the report. Within the appendices there are sections for safety, demographics, efficacy, etc.

BI have also introduced a corporate standard for the format and layout of the figures, tables, listings and statistical documentation which are included in the report and in its appendices. Amongst the requirements are a landscape display area with a portrait header (giving the page number, trial identification number and country producing the report), margins which enable the report to be copied onto A4 or US letter size paper without any of the display area being lost, soft scanning directly from the output file and independence of the programming environment.

BI use SAS as the reporting tool to display and summarise the clinical trial data. The appendices to the report are printed from SAS whilst the accompanying text part of the report is written using Microsoft Word®.

The base printing and page numbering of SAS output is not one of the SAS System®'s strongest features; hence after the introduction of the new standards in a corporate SOP in 1993, a number of methods to meet them were employed. These varied from the use of SAS forms followed by photocopying, photoreduction, scanning (Xerox Docutech) and importing all the SAS output into Microsoft Word®. These solutions either did not meet the SOP format fully or proved to be too labour intensive and costly to implement.

Our complete solution takes three parts; a macro to include SAS tables into Microsoft Word® as a Word table, SAS graphics device drivers to create graphs for inclusion into Microsoft Word® and the appendices and a SAS/AF® application to meet our documentation needs and to standardise the layout and numbering of the data displays and summaries. In this paper we will be concentrating on this later aspect of report production.

PRINT MACRO (PM) AND ASSOCIATED PROGRAMS

The Print Macro (PM) is an application which calls a set of user-written SAS programs and allows the output to be formatted as the appendices of a clinical study report.

The application was developed to meet a number of requirements from the company concerning the patient data listings, tabulations and graphs which form some of the appendices to a clinical study report.

The requirements were:

- landscape page
- a portrait header containing the page number preceded by a prefix indicating the section of the report, the trial number and the country which produced the report
- standardised margins to accommodate European and US letter page sizes
- standardised position and content of titles and footnotes
- graphs presented together with their associated tables and listings
- table of contents (page numbers and titles)
- documentation of which program was used to produce each page of the report
- facilitation of the reuse of programs
- storage of an electronic copy of the logs and output from each user program
- storage of an electronic copy of the report.
- soft scanning directly from the output file

- independant environment for the programming

The PM provides an attractive output, whilst reducing the time and manpower involved. It is currently being used by BI in Canada, US, UK, France and Germany. It is also used by several contract research organisations in Europe. It has been used successfully for over 100 clinical trials and is currently in use for a further forty trials.

The PM allows the user to:

- package together the SAS programs for a particular study report
- run them (or any subset) as a batch
- save the output and log automatically
- sort the SAS outputs into the desired order for the report
- print the report appendices with a portrait header containing the page number and other required information.
- produce an output file in Postscript® format ready for soft scanning or inclusion in Documentum® for publishing.

A table of contents is produced automatically.

Examples of the printed output (a graph and a table of contents) are given in the appendix.

The SAS outputs can be those produced by the Base SAS, SAS/Graph® or SAS/Stat® procedures or ASCII output from any other package. The report can contain non-printable sections (the page numbering is adjusted accordingly and entries for these sections are included in the table of contents).

The user enters information about each of his programs in a SAS data set. We have termed this data set the meta data set.

PM uses the meta data set to control the selection of the programs to be run and the outputs to be printed, the content of the titles and footnotes and the names and location of the output and log produced by each user-written SAS program. The meta data set also contains the information required for the table of contents and for the programming documentation.

The information about each user-written program is stored as a record (or several records if the program produces more than one output) in the meta data set. The information required is the appendix number, title, footnote, program name, output storage location, whether or not the program is to be run, whether or not the output is to be printed and the number of pages to skip if the output is a non-printable section.

A user interface was written using SAS/AF®. Once the user has written the reporting programs he can produce the report appendix by clicking on the various options. Frame entries and methods are used to control the creation and printing of output.

From a SAS session access to PM is obtained by clicking on a tool bar icon. The user is then taken into the Study Selection Screen to choose the study on which he needs to work. Having chosen a study a menu with four main task options is displayed.

The tasks are:

- Edit Meta Data Set and/or View Output and Logs
- Run User-Written Programs
- Print Report Appendix
- Produce Program Documentation.

EDIT META DATA SET AND VIEW OUTPUT AND LOGS

The PM checks whether a meta data set exists and if not creates it in the appropriate directory for the study.

The user can search for, edit or add records in the meta data set using the SAS/FSP® FSEDIT menu. If the record is for a program which has been run already then the date is shown and the user can view the log and output.

PM uses field attributes and screen control language to ensure that the entries are valid and in the required case.

RUN USER-WRITTEN PROGRAMS

Programs can be stored as either external ASCII files or as SAS catalog entries.

PM displays the default directory where the programs for the study are stored. This can be overwritten if required. Alternatively the user can click on a Frame object which takes the user through the directory structure allowing him or her to choose one of the available directories.

The user selects the appendices to be run by clicking on a check box. A subset of the programs can be run by entering a WHERE clause. Example WHERE clauses can be viewed by clicking on a drop-down list. In addition variables which can be used in the WHERE clause (i.e. those in the meta data set) are displayed with their labels in a window which can be scrolled. PM uses the appendix selection and the WHERE clause (if any) to create a subset of the meta data set. PM then

uses the program name field in the meta data set to retrieve each program for processing.

Before each program is run, PM redirects the output to the location specified in the meta data set and the log to a catalog entry.

PM then copies each program into the SAS/AF[®] preview window and submits it.

Whilst the programs are running the user can switch to the log window which displays which user written program is currently executing. When each user program finishes, a message is displayed indicating whether there were any errors in the last Proc (using the SAS macro variable &syserr). (Only errors in the last procedure are detected as SAS resets &syserr at the start of each new procedure and data step.) If there is an error the user can view the log from the FSEDIT screen.

PRINTING THE APPENDICES

An Postscript[®] printer is required.

The user clicks on the appendix to be printed. He can choose whether to print the entire appendix, a section of pages (by specifying the first and last page) or just the table of contents. Optionally an electronic copy can be stored. Currently users are limited to 99,999 pages per section.

PM creates a subset of the meta data set containing the records for the appendix to be printed. The records are sorted into the correct order for the final report. PM then reads each non-graphics output into a temporary SAS data set. (If the output is stored as a catalog entry then this is achieved either using the CATALOG option of the FILENAME statement (SAS version 6.12) or by copying the catalog entry into the notepad window where it is saved as an ASCII file (SAS ver 6.08). The SAS macro variable &SASVER is used to direct the program flow as required.)

PM assigns page numbers to each record and stores the first record from each output for use in the table of contents. Postscript[®] codes are added to set page orientation, font sizes and to position the portrait header.

PM handles graphs differently from other output to be printed.

The number of pages to skip to allow for graphs is calculated by using the CONTENTS statement of PROC CATALOG to create a temporary data set for the graphics catalog specified in the meta data set. The temporary data set contains one record per catalog entry and therefore has one record per graph. The number of records is then counted and used to determine the number of pages to skip. This

information, together with the title from the meta data set, is used for the table of contents entries for the graphs.

PM sorts the SAS graph catalog entries into the correct order (the order in which they were produced within the graph procedure) using the SQL DICTIONARY.MEMBERS table variable ALIAS. Previously when we used the PCL[®] version of PM, then PM would use the GSLIDE procedure to produce the portrait header (including the page number) for each graphics page. PM then used the GREPLAY procedure and a graphics template to combine each landscape graph with its portrait header and saves the complete graphics page as a catalog entry called Page*n* (where *n* is the page number). The graphics pages were either stored in the work directory or in one of the study directories, depending on whether or not the user requested that an electronic copy be saved. To print the graphics pages, PM used Proc GREPLAY to save each page as a graphics stream file. PM then copied the file to the printer.

Now that the Postscript[®] version of PM has been developed the final graphs are produced as a Postscript[®] file (one file per page) which are incorporated into one large Postscript[®] file for the complete appendix when the section is run.

The non-graphics pages are saved as an ASCII file preceded by the table of contents. Postscript[®] code is used at the beginning and end to switch the printer to Postscript[®] mode and to reset it afterwards.

DOCUMENTATION OF PROGRAMMING

The user selects the appendices for which documentation is required by clicking on one or more check boxes. A list of the programs used to create the outputs is produced using Proc REPORT and sent to the SAS output window where it can be viewed and printed. The landscape title and trial data dictionary tables used to produce the output given in the selected appendices are displayed together with the program name.

This listing is very useful for ensuring that the titles are correct and in the right order.

SITE INSTALLATION

A site installation screen is provided for system supervisors to set the default values for the site identifier, printable page size, margins, line spacing, graphics driver, graphics printer port, default names of sub directories of each study where the programs and outputs are stored, location of the studies

definition data set and any libname options required to use a SAS SHARE® engine.

In order to access PM each user needs to add an icon to their toolbar, for example by using the Edit Tools option of the SAS Options menu.

MODIFYING SAS AUTOEXEC PROGRAMS FOR USE WITH PM

In order to use PM, the libref PRTMACRO must be assigned to point to wherever the PM application is stored.

Users may prefer to run and test individual user programs outside PM before running them from PM for the final report. In SAS 6.12 filename statements can be used to access the PM catalog entries without going into PM.

MODIFYING USER PROGRAMS FOR USE WITH PM

In order to access the titles and footnotes specified by the user in the meta data set, each user program must contain the following statements before the procedure which creates the output.

```
%LET PROGNAME=progrname.sas;
```

```
%INC TITLES;
```

where *progrname.sas* is the name of the user program.

For graphs %INC TITLES; is replaced with %INC GTITLES1; (for graphs to be stored as SAS catalog entries) or %INC GTITLES2; (for graphs to be stored as Microsoft Word® computer graphics metafiles).

If the program is used to produce more than one output then the statement %LET OUTPUTNO=*n*; should be inserted before %INC TITLES; in order to obtain the correct title and footnote (where *n* is an output number entered into the meta data set).

Graphs to be printed using PM should be saved as SAS catalogs e.g. by using the GOUT=*output-catalog* option on the SAS/Graph® PROC statement.

VALIDATION

In order to be certain that none of the text on the original outputs is changed or lost, validation was built in to the application from the outset e.g. if the page size of an individual output is longer than that set on the site installation screen, then each page of the original output will be split into two pages.

PLATFORMS

The PM works on all PC versions of SAS and on all Postscript compatible printers (HP range, Compaq, etc.). It is currently being used with Netware® 3.1x, Netware® 4.1x and Windows (NT & W4WG) network.

The front end was originally written for SAS version 6.11 and modified to allow 6.08 compatibility. It is now available as a SAS version 6.12 application.

WHAT ARE THE BENEFITS OF USING THIS SYSTEM?

We have found the benefits to be

- integrated system with user front end

Reports are run and printed with only a few key strokes and are produced very quickly after the treatment codes for the study are unblinded.

- facilitates standardisation of page layout and titles

Corporate standards are adhered to both by Boehringer Ingelheim employees and in co-operative ventures with contract research organisations and other pharmaceutical companies

- facilitates standardisation of physical storage locations

PM provides the default storage location.

- reports are produced the way the users are used to doing it

It is easy to incorporate existing programs into PM.

- allows the user to keep track of and plan the programs to be used for reporting the study

PM makes it easier for the user to go back to a study which he has not worked on for a while and continue from where he left off.

- provides a starting point for new studies

For a new study the user can copy the meta data set and programs from a similar study and customise them.

- the appendices are produced all in SAS

No interfacing required and users only have to know one package.

- the output file (Postscript®) can be soft scanned to convert to images

Interface Documentum and software converters.

- the environment in which each program runs is independant, thus ensuring an

easier environment to validate in and to provide for use in CANDAs

Change in programming style required but this further helps in obtaining one programming style for Boehringer Ingelheim.

ACKNOWLEDGEMENTS

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APPENDIX

Example of a Graph Printed Using PM

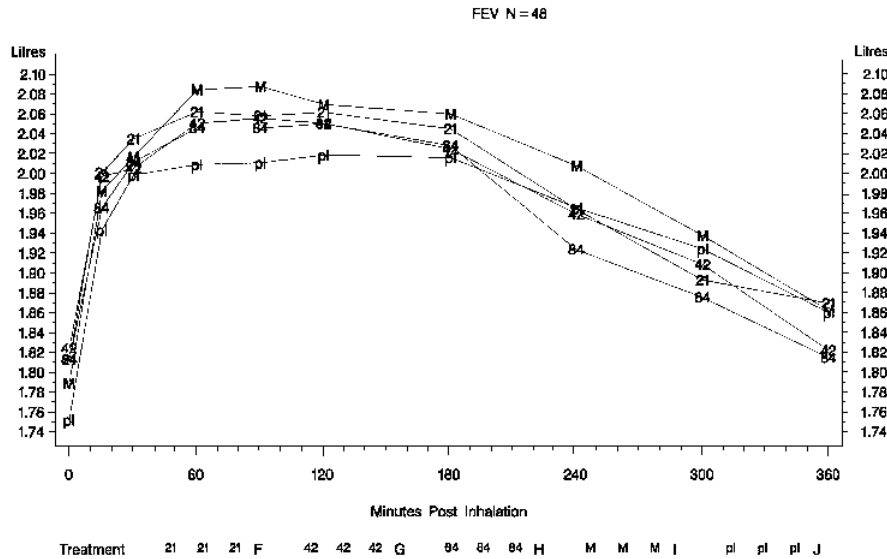


FIGURE 4.2 FEV1, Time-Response Curves, Uncorrected for Pre-dose, Intent-to-Treat Data Set

Source Data: Appendix 15.9.2. LISTING 4.1

g_spirot.sas 15FEB96

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Appendix 15.9.2, FIGURE 4.2

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Example of the Table of Contents Produced by PM

Page	Table of Contents
1	LISTING 1.1 Major Protocol Violations
3	LISTING 1.3 Evaluability for Analysis
5	FIGURE 4.1 Pre-Inhalation FEV1
6	FIGURE 4.2 FEV1, Time-Response Curves, Uncorrected for Pre-dose, Intent-to-Treat Data Set
7	FIGURE 4.3 FVC, Time-Response Curves, Uncorrected for Pre-dose, Per-Protocol Data Set
8	FIGURE 4.4 FEV1, Time-Response Curves by Centre (Change from Pre-Dose in Litres, Per-Protocol Data Set)
12	FIGURE 4.5.1 FEV1, Time-Response Curves by Steroid Dose (Change from Pre-Dose)
13	FIGURE 4.5.2 FEV1, Time-Response Curves by FEV1/FVC % at Screening (Change from Pre-Dose)
15	FIGURE 4.5.3 FEV1, Time-Response Curves by Pre-Dose % of Predicted FEV1 at Screening (Change from Pre-Dose)
18	FIGURE 4.5.4 FEV1, Time-Response Curves by Reversibility at Screening (Change from Pre-Dose)
24	FIGURE 4.5.5 FEV1, Time-Response Curves by Age (Change from Pre-Dose)
26	FIGURE 4.6.1 FEV1 Max(0-6 hours), Uncorrected for Pre-Dose (Litres)
27	FIGURE 4.6.2 FEV1 AUC(0-6 hours), Uncorrected for Pre-Dose (Litres)
28	FIGURE 4.6.3 FEV1 AUC(0-6 hours), Uncorrected for Pre-Dose (Litres)
29	FIGURE 4.6.4 FEV1 AUC(4-6 hours), Uncorrected for Pre-Dose (Litres)
30	FIGURE 4.6.5 FEV1 Max(0-6 hours), Change from Pre-Dose (Litres)
31	FIGURE 4.6.6 FEV1 AUC(0-6 hours), Change from Pre-Dose (Litres)
32	FIGURE 4.6.7 FEV1 AUC(0-6 hours), Change from Pre-Dose (Litres)
33	FIGURE 4.6.8 FEV1 AUC(4-6 hours), Change from Pre-Dose (Litres)
34	FIGURE 4.6.9 FEV1 Max(0-6 hours), Percentage Change from Pre-Dose
35	FIGURE 4.6.10 FEV1 AUC(0-6 hours), Percentage Change from Pre-Dose
36	FIGURE 4.6.11 FEV1 AUC(0-6 hours), Percentage Change from Pre-Dose
37	FIGURE 4.6.12 FEV1 AUC(4-6 hours), Percentage Change from Pre-Dose
38	FIGURE 4.7 FEV1, Time-Response Curve (before the use of the estimation algorithms)
39	FIGURE 4.8 Individual Patient, FEV1, Time-Response Curves (Litres)
105	FIGURE 4.9 Individual Patient, FEV1, Time-Response Curves (Percentage Change from Pre-Dose)
189	TABLE 4 Number of Patients for whom an FEV1 was recorded

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Appendix 15.9.2, Table of Contents